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INFORMATION REPORT

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A. VEB Jenapharm - general

1. VEB Jenapharm, Otto-Schott-Strasse 13, Jena, is directly subordinate to the Staatssekretariat fuer Chemie, Steine und Erden.

2. Professor Dr. med. Hans Knoell, scientific head of Jenapharm, is, in addition, director of the Institut fuer Mikrobiologie, Jena, which is also on Otto-Schott-Strasse. This institute is listed as an institute of the University of Jena in the current catalogs of that University. Jenapharm also occupies a building on Muehlenstrasse in Jena, in which large-scale production of streptomycin is due to start on 1 September 1952.

3. Space is so limited at Jenapharm that, in 1950, it was decided to retain production in the old buildings but to transfer all research work to Beuthenberg, a suburb of Jena. Three million DM East were then voted for new construction in Beuthenberg, and a new Institut fuer Mikrobiologie und experimentelle Therapie, under Hans Knoll, is now being built there. This institute will be directly responsible to the DDR Ministry of Health. It is expected that some of the new buildings (some laboratories and animal houses) will be taken over in September 1952. The complex will not be finished until 1954.

4. Jenapharm has also built a new BCG (Bouet-Calmette-Guérin) institute on the Beuthenberg premises. BCG vaccine will be produced here. In mid-April 1952, it was expected that this institute would be ready within a matter of days.

5. As of April 1952, the heads of the various departments of Jenapharm were:

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Business manager	:	Bornschein (fnu)
Technical "	:	Dr. Koehler
Scientific head	:	Professor Hans Knoell
Pharmacy Department	:	Dr. Greulich, head ; Dr. Hummel, deputy
Chemistry Department	:	Dr. Richard Weinhold, head
Biophysical Department	:	Dr. Bauer, head
Total Staff	:	1,700

6. The main products of Jenapharm are:

BCG vaccine
Tuberculin preparation (tebethion)
Depot (sic) penicillin
Penicillin
Jenacain (local anaesthetic) (procaine)
Jecoffin and sandestin (analgesics)
Vitamin preparations
Pain relieving media (morphine hydrochoricum)
Narcotics (Isomodrine)
Circulatory remedies (Kreislaufmittel)
Nicotinamide (dermatosis, allergies, enteritis, colitis)
Dimitan and trimitan (anti-tumor substances)
Chloronitrin (large scale production officially starts 1 June 1952)
Streptomycin (large scale production due to start on 1 September 1952)

7. Individual research

(a) Present work includes that of Dr. Zapf, specialist in microphotography and ultrasonics. He is conducting research on the influence of ultrasonic radiation on bacilli in the presence of penicillin, streptomycin or chloronitrin.

(b) The recent work of Dr. Greulich and Dr. Jagemann is described more fully below.

B. The production of chloronitrin[1]

1. Chloronitrin is an optically active form of synthetic chloromycetin. It is dl-threo-1-p-nitrophenyl-2-dichlor-acetylamino-propandiol (1,3). It is the synthetic form of the antiobiotic from Streptomyces venezuelae.[2]

2. In May 1952, chloronitrin was being synthesized by Jenapharm by a 12-stage process worked out by Professor Drefahl.[3] The chloronitrin laboratory was under the direction of a Dr. Greulich. Large scale production, officially due to start on 1 June 1952, was already beginning in April 1952.

3. Chloronitrin is an optically active substance. Professor Drefahl started from a halogen-substituted acetophenone and converted this in the usual way to the corresponding aminoketone: the latter is then transformed by condensation and hydrogenation to a propanediol derivative. Under controlled conditions, the isomers formed will then separate. The active isomer is then nitrated and the reaction product - for chloromycetin has two asymmetric C atoms - is separated with tartaric acid into its optically active components. The relevant stereoisomer is then converted to the end product with dichloracetic acid.

4. In early 1952, chloronitrin was issued by Jenapharm for clinical trials in gelatine capsules, each containing 250 mgs.

5. A racemic form of chloronitrin is also produced by Jenapharm.

6. Certain unspecified alterations to the laboratory method of chloronitrin production, outlined in (c) above, had to be made by Jenapharm before they could put it into commercial production.

C. Research on streptomycin production[4]

1. Dr. Jagemann of Jenapharm VEB, Jena, has been one of the specialists most concerned with the experimental production of streptomycin at that firm. In April 1952, he wrote a report for the DDR Ministry of Health on his research experiences. The following contains everything of scientific interest in Dr. Jagemann's report.

2. Dr. Jagemann pointed out in his report that the production of streptomycin, after the fermentation process, normally comprises five stages:

   (a) separation of the mycelium by filtration.

   (b) extraction of the streptomycin by adsorption on activated charcoal (aktive Kohle).

   (c) washing of the streptomycin from the charcoal adsorption product.

   (d) concentration of the streptomycin.

   (e) precipitation of the solvent and subsequent filtration and drying.

   It is then necessary to purify the streptomycin further by a comparatively complex process.

3. The author then described the individual operations, with particular reference to differences from previous experience in this field:

   (a) Separation of the mycelium.

      1. In almost all publications available to Jenapharm, it was stressed that the separation of the mycelium was particularly difficult, because the mycelium, by its slimy nature, tended to block up the filters. The Americans stated that they had only been successful by using a continuous pressure filter system. Experience at Jenapharm showed that even with the aid of filter promoting substances (Filterhilfsstoffen), proper separation could not be achieved. Jenapharm then searched for an alternative method; it hit on centrifuging the material. The first successes were achieved with a bowl centrifuge (Schaelzentrifuge).

      2. This type of centrifuge possesses a closed canister (Korb), on whose walls the mycelium is deposited, while the clear culture solution is drawn off with the aid of a bowl tube (Schaelrohr). The only disadvantage of this system is of course that it is discontinuous.

      3. The recently developed sludge separator (Schlamm-Schleuder) and cider separator (Mostseparator) now on the market are similar in principle to the bowl centrifuge. They consist of several closed, concentric, cup-shaped centrifuge parts, fitted together one inside another. The solution to be clarified goes first into the innermost centrifuge compartment. Solid particles are thrown down onto the wall of the centrifuge compartment, and the clarified solution, after filling the centrifuge compartment, goes over into the next larger

compartment. This is repeated several times. The filtrate so prepared is optically clear and very satisfactory. These two separators operate continuously. Until April, Jenapharm had only worked with small experimental separators. It was intended to install cider separators with a capacity of 400 liters/hour.

(b) Extraction by adsorption. The clear culture filtrate was treated with 1% activated charcoal, which adsorbs the streptomycin from the solution. The charcoal was separated with a sling centrifuge (Schleuderzentrifuge) and washed with methanol to remove impurities. Dr. Jagemann recommended a repetition of this process, to avoid loss of streptomycin. This stage of the process was carried out by Jenapharm without difficulty the usual way.

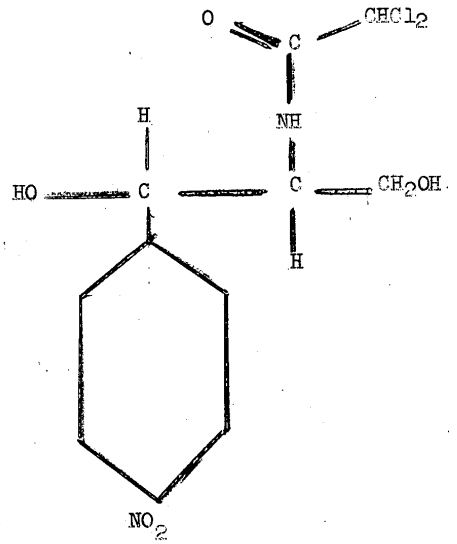
(c) Removal of streptomycin from the charcoal. Again, this stage was carried out by Jenapharm in the usual way. The streptomycin is washed out of the charcoal filter cakes (Kohlefilterkuchen) with the aid of a 1% methanol acid salt solution. Streptomycin hydrochloride is formed; this goes into solution, while a large part of the impurities remain adsorbed to the charcoal. The charcoal is again separated on a sling centrifuge (gummed).

(d) Concentration of the extracted product. The product washed out of the adsorbent charcoal is then normally concentrated before the precipitation of the raw streptomycin. According to available American literature, the strongly acid product washed from the charcoal is first neutralized and then concentrated through a single stage evaporator working in a vacuum and under a relatively low temperature (60° or less). The concentrate then contains about 25% solid matter. In contrast to this, Jenapharm developed a process for treating the product washed from the charcoal without preliminary neutralization. Concentration of the acid salt was carried out in glass vacuum rotary evaporators (Vakuum Umlauf-Verdampfer) supplied by VEB Schott, Jena.5 Compression was carried out at a temperature of less than 30°, in vacuo, so as not to destroy the streptomycin. As soon as the original solution was reduced to about 1/20th of its volume, it was thinned with an equal volume of water and again concentrated under similar conditions, until no more methanol came off.

(e) Precipitation of the solvent, with subsequent filtration and drying. The streptomycin is normally then precipitated by the addition of another solvent, e.g. amylacetate or ether. The raw streptomycin is then filtered off and dried in a vacuum dryer. Jenapharm's experience, however, was that it was superfluous to precipitate the streptomycin by a solvent, because, as a result of the previous stage treatment, only an aqueous solution of streptomycin hydrochloride exists. This contains only coloring matter and a small amount of salts, apart from the hydrochloride. On the other hand, using the normal neutralization method mentioned above, far more salts are contained in the product. Jenapharm's aqueous concentrate is immediately dried in vacuo. In this way, Jenapharm obtained crude salts of streptomycin hydrochloride with an active content of 200-300 international units. Further purification of the crude salts was carried out by further solution in methanol and treatment with aluminum oxide. After filtering off the aluminum oxide, amylacetate is slowly added to the clarified solution until a distinct turbidity has set in. The streptomycin hydrochloride then separates after a short time as a flocculent precipitate which is filtered off and dried. This precipitation process is repeated two or three times. Jenapharm succeeded in this way in producing amorphous streptomycin salts with an active content of 600-700 international units.

25X1 1. [redacted] Comment: This appears to be ZAFT task 510513/05861 - Versuche zur Synthese des Chloromycetins. ZAFT gave the assignment, the preparations of a scientific report on this subject, to Dr. R. Weinhold, with a vote of 50,000 DM East and a time limit of the fourth quarter of 1951.

25X1 2. [redacted] Comment: The structure of chloronitrin would appear to be:



25X1 3. [redacted] Comment: Probable trace: Prof. Dr. phil. Guenther Drefahl (born Rostock 11 May 1922) organic chemist and biochemist, Friedrich-Schiller University, Jena.

25X1 4. [redacted] Comment: This appears to be ZAFT task 510513/06441 - Betriebstechnische Versuche zur Streptomycingewinnung im Submersverfahren, zur Reinigung von Roh-Streptomycin und der Herstellung Kristallinen Streptomycins: 150,000 DM East, later 410,000 DM East, to be finished by the fourth quarter of 1952.

25X1 5. [redacted] Comment: This firm is Jenaer Glaswerk VEB (formerly Schott und Genossen), Jena, Otto-Schott-Strasse 9, VVB Optik.